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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/766,362	01/19/2001	Solomon S. Steiner	1951300.00047	8907

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EXAMINER	
SHEIKH, HUMERA N	
ART UNIT	PAPER NUMBER
1615	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/766,362	STEINER ET AL.	
	Examiner	Art Unit	
	Humera N. Sheikh	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,7,8,10-12,14,16-18,20 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7,8,10-12,14,16-18,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Receipt of the Request for Continued Examination (RCE) under 37 C.F.R. §1.114, the Amendment, Applicant's Arguments/Remarks and the NPL Article (Respiratory Drug Delivery, VIII, 2002), all filed 01/21/09 is acknowledged.

Claims 1, 3-5, 7, 8, 10-12, 14, 16-18, 20 and 21 are pending in this action. Claims 1, 3, 7, 14 and 20 have been amended. Claims 2, 9 and 15 have been cancelled herein. 6, 13 and 19 were previously cancelled. Claims 1, 3-5, 7, 8, 10-12, 14, 16-18, 20 and 21 are rejected.

Note: Applicants have now amended claim 1 to include the limitation "..are sized such that the particles are preferentially retained in the nasal cavity and" in lines 5-6. The amendment has not been properly introduced since Applicants have not underlined this limitation demonstrating that it is newly added subject matter. In any event, this new limitation has been noted and considered.

* * * * *

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 21 January 2009 has been entered.

* * * * *

Information Disclosure Statement

The information disclosure statement (NPL Article - Respiratory Drug Delivery, VIII, 2002) submitted 21 January 2009 fails to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. The information disclosure statement has been placed in the application file, but the information referred to therein has not been considered.

* * * * *

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because the limitation, "…suitable for administration of a drug" in line 2, renders the claim confusing. It is unclear as to whether Applicants are referring to the 'antihistamine' for administration to the nasal region or some other medicament. Clarification is requested.

Claim 1 recites the limitation "*a drug*" in line 2. There is insufficient antecedent basis for this limitation in the claim.

The term "preferentially" in claim 2 is a relative term which renders the claim indefinite. The term "preferentially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The metes and bounds of the term cannot be reasonably ascertained. It is suggested that this term either be positively recited or deleted.

* * * * *

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 3-5, 7, 8, 10-12, 14, 16-18, 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Steiner *et al.* (hereinafter "Steiner") (U.S. Pat. No. 5,503,852) in view of Illum (US. Pat. No. 5,690,954).

Steiner *et al.* ('852) teach drug delivery systems based on the formation of diketopiperazine microparticles and microencapsulation of drugs by derivatives of diketopiperazine, wherein the microparticles are formed in the presence of the drug to be delivered and are between 0.1 to 10 microns in diameter and whereby the microparticles are used for diagnostic applications for imaging of the nasal tract (see reference col. 4, lines 30-55); (col. 10, lines 25-49); (col. 13, lines 13-24) and Abstract.

According to Steiner, biologically active agents having therapeutic, prophylactic or diagnostic activities can be delivered and include active agents, such as hormones, vasoactive agents, anesthetics or sedatives, steroids, decongestants, antivirals, antisense, antigens, antibodies and the like (col. 10, lines 25-49).

Steiner *et al*. teach a system based upon diketopiperazine or one of its substitution derivatives, including *diketomorpholines and diketodioxanes*. The diketopiperazine synthetic intermediates are preferably formed by cyclodimerization to form diketopiperazine derivatives at elevated temperatures under dehydrating conditions, functionalized on the side chains, and then precipitated with drug to be incorporated into microparticles (see abstract; col. 4, lines 49-67; col. 7, lines 8-11).

The protective material, the diketopiperazines, are not biologically active and do not alter the pharmacologic properties of the therapeutic agents (col. 11, lines 1-3).

The instant invention is drawn to a composition for the nasal administration of a drug in dry powder form for administration to the nasal region, whereby the dry powder comprises microparticles having a particle size of 10 to 20 microns and comprising drug and a diketopiperazine. There is no patentable distinction observed between the instant invention and

the prior art since the prior art teaches drug delivery systems based on the formation of diketopiperazine microparticles and microencapsulation of drugs by derivatives of diketopiperazine, wherein the microparticles are between 0.1 to 10 microns in diameter and are used for nasal applications. Steiner explicitly teaches that their microparticles can be between 0.1 and 10 microns. Thus, the '10 micron' size microparticles disclosed by Steiner overlaps with the "10 microns" claimed herein by Applicant and hence the "10 microns" of Steiner satisfies the claim limitation requirement of "10 to 20 microns". The 10 microns taught by the prior art is an overlapping particle size that falls within the range of "10 to 20 microns" instantly claimed and thus reads on the instant particle size limitations. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). In this case, Applicants have not established that their claimed range provides for unexpected results over the ranges disclosed by the art. Moreover, Applicant themselves assert that "about 10 microns" would be a suitable micron size in order for the particles to remain in the nasal cavity.

Furthermore, Applicants have not demonstrated that the "10 micron" size range claimed is a critical lower limit. This is evidenced by Applicant's own specification. For instance, formulations I and II on pages 13 and 14 demonstrate particles with micron sizes that are less than 10 microns. More specifically, formulation I on p. 13 demonstrates that 10% of particles had a particle size of only *3.15* microns. Similarly, Formulation II on page 14 demonstrates that 10% of particles had a particle size of only *2.99* microns. Therefore, this clearly establishes that the 'between 10 microns' claimed by Applicants is not a critical lower maximum particle size

limitation. The determination of a suitable or effective particle size is within the level of one of ordinary skill in the art, based on routine experimentation. Regarding the instant method of administering a dry powder comprising microparticles, one of ordinary skill in the art would have been motivated to nasally administer the microparticles of Steiner that comprise a drug and diketopiperazine and further optimize, if necessary, the particle size or size range for the intended application (i.e., nasal applications). One would be motivated to do this with a reasonable expectation of success of obtaining an enhanced drug delivery system that effectively (nasally) administers the microparticles in the (nasal) cavity for maximum treatment. Regarding the limitation of "wherein the composition does not pass into the pulmonary system", recited in instant claims 1, 7 and 14, it is the position of the Examiner that the 10-micron sized microparticles of Steiner, which overlap with the "about 10 microns" instantly claimed would be retained in the mucosal cavity for sufficient drug delivery and would not pass into the pulmonary system and thus, would be suitable for their intended purpose. Thus, this teaching of the "10 micron-sized" microparticles of Steiner meets this limitation requirement. Absent a showing of evidence to the contrary, Steiner's microparticles would also be retained in the nasal cavity as Steiner teaches that their microparticles are suitable for nasal administration.

Regarding Applicant's limitation of "wherein more than 50% of the particles have a size greater than about 10 microns", it is the position of the Examiner that Applicant presents no data establishing that the 50% particle size limitation would be an improved result over the presence of the smaller micron-sized particles of the art. Moreover, Steiner teaches microparticles that include 10 microns in diameter and thus recognizes an overlapping particle size with that of the instant claims.

As stated above, biologically active agents disclosed include those having therapeutic, prophylactic or diagnostic activities can be delivered and include active agents, such as hormones, vasoactive agents, anesthetics or sedatives, steroids, decongestants, antivirals, antisense, antigens, antibodies and the like (col. 10, lines 25-49).

With respect to the limitation "suitable for administration of a drug" in claim 1, it is noted that "drug" has not been defined in the specification. Thus, the term has been given its broadest reasonable interpretation.

Steiner does not teach an antihistamine (*i.e.*, chlorpheniramine) and a device for nasal administration (i.e., nasal insufflator).

Illum ('954) teaches a drug delivery system for *nasal administration* of an active drug in *dry powder form* wherein the drug delivery system comprises microsphere particles formed of active drugs that include *antihistamines*, vasoconstrictors, anti-inflammatory agents and anesthetics whereby the composition is administered in the form of a dry powder having a particle size of from about 10 microns to about 100 microns (see reference column 5, line 14 through col. 6, line 53); (col. 9, lines 24-61). (The range of about 10 microns to about 100 microns taught by Illum encompasses the range of "10 to 20 microns" claimed by Applicant).

Suitable active drugs disclosed are anti-inflammatory agents, vasoconstrictors, anesthetics (analgesics) and antihistaminic agents. Antihistaminic agents are diphenhydramine hydrochloride, *chlorpheniramine maleate* and clemastine. The microspheres are administered via the nasal route using a *nasal insufflator device*. Examples of these are already employed for commercial powder systems intended for nasal application (*e.g.*, Fisons Lomudal System); (col.

8, line 44 through col. 9, line 60). The teaching of a (nasal insufflator) device meets the limitations of a device as recited in instant claims 7-12.

Illum teaches that the drug to be administered to a mucosal surface such as the *nose*, eye, etc., can be administered as a powder and can also be administered in the form of a colloidal particle comprising a microsphere system (col. 5, line 14-26).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the antihistamines (*i.e.*, chlorpheniramine) as taught by Illum within the microparticulate formulations of Steiner. One would be motivated to do so with a reasonable expectation of success because Illum teaches a nasally administered drug delivery system and device (nasal insufflator) comprising antihistamines, such as those claimed (chlorpheniramine), which are effective medicaments useful for treating allergic conditions, administered via nasal administration and provided in a dry powder form for sufficient drug delivery to the nasal mucosa. The expected result would be an improved microparticulate drug delivery system for nasal administration, useful for treating allergy symptoms.

Hence, the instant invention, when taken as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, given the explicit teachings of Steiner in combination with Illum.

Response to Arguments

Applicant's arguments filed 01/21/09 have been fully considered and were found partially persuasive.

- **Rejection under 35 U.S.C. §103(a) of claims 1, 2, 4, 5, 7, 9, 11, 12, 14, 15, 17 and 18 over Steiner et al. (US Pat. No. 5,503,852) and Rejection under 35 U.S.C. §103(a) of claims 3, 8, 10, 16, 20 and 21 over Steiner et al. (USPN 5,503,852) in view of Illum (USPN 5,690,954):**

Applicant argued, "Steiner does not teach or suggest that the microparticles could be used to deliver drugs to the nasal cavity as therapeutics and makes no suggestion that the microparticles could be used with antihistamines as claimed herein."

This argument was found persuasive by virtue of the amendment which incorporates and replaces "drug" with "antihistamine" in all independent claims. Accordingly, the rejection over Steiner alone has been withdrawn. The rejection has been reformulated as Steiner in view of Illum. Illum demonstrates the teaching of employing antihistamines in a drug delivery system for nasal administration of an active drug in dry powder form. The drug delivery system comprises microsphere particles formed of active drugs that include antihistamines, whereby the composition is administered in the form of a dry powder having a particle size of from about 10 microns to about 100 microns. See column 5, line 14 - col. 6, line 53; col. 9, lines 24-61. Suitable antihistaminic agents include chlorpheniramine maleate. The microspheres are administered via the nasal route using a nasal insufflator device. See col. 8, line 44 through col. 9, line 60. Thus, the secondary reference sufficiently fills the deficiency of the primary reference based on the former's teaching of delivering antihistamines in dry powder form to the nasal cavity, using a nasal insufflator device.

Applicant argued, "Applicants have established that particles which are predominantly smaller than 10 microns in size, pass through the nasal cavity and into the pulmonary system.

Example 5, comprising a diketopiperazine and an antihistamine and from 1-20 microns in size, did not cause a bitter aftertaste after administration, confirming that they are retained in the nasal cavity."

This argument was not persuasive. While particles smaller than 10 microns in size may proceed into the pulmonary system, it is noted that Steiner's particles, which are taught to include 10-microns overlap with the "about 10 microns" instantly claimed. Thus, the 10-micron sized particles of Steiner would also be retained in the mucosal cavity for sufficient drug delivery and would not pass into the pulmonary system. The particles of Steiner would further not cause a bitter taste, since they would be retained in the nasal cavity. Hence, the particles of Steiner would be suitable for their intended purpose (i.e., administration to the nasal cavity).

Applicant's arguments regarding the Wilson *et al.* Publication have not been considered. The NPL document has not been properly cited and submitted on an Information Disclosure Statement and thus, has not been considered on the merits.

Applicant argued, "Illum does not disclose microparticles comprising diketopiperazines and the combination of Steiner and Illum does not teach or suggest the nasal administration of microparticles between 10 and 20 microns in size which do not pass into the pulmonary system upon nasal administration."

These arguments were not rendered convincing. The drug delivery systems of Steiner are based on the formation of diketopiperazine microparticles and microencapsulation of drugs by derivatives of diketopiperazine. Steiner discloses particles between 0.1 to 10 microns in diameter. The 10 micron-sized particles of Steiner overlap with the "10 microns" claimed herein by Applicant and thus would be retained in the nasal cavity and would not pass into the

pulmonary system. Steiner discloses that their particles are used for diagnostic applications for imaging of the nasal tract. Applicant's argument that "Illum does not teach microparticles comprising diketopiperazines" was not persuasive since the primary reference of Steiner initially teaches the microencapsulation of drugs by derivatives of diketopiperazines and thus meets this limitation requirement. Both references demonstrate the teaching that their particles are used for nasal administration. Illum further recognizes dry powders having a particle size of from about 10 microns to about 100 microns, which clearly encompasses and overlaps with the particle size instantly claimed (between about 10 microns and about 20 microns). In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). See also *In re Peterson and In re Geisler.*

The rejections of record have been maintained.

Conclusion

--No claims are allowed at this time.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (571) 272-0604. The examiner can normally be reached on Monday-Friday during regular business hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Humera N. Sheikh/

Primary Examiner, Art Unit 1615

hns

April 1, 2009